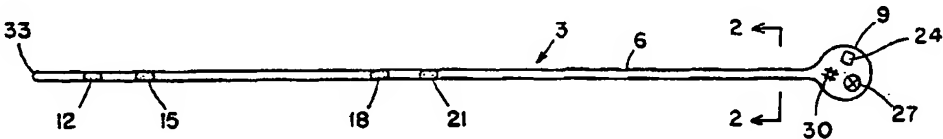


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(21) International Application Number: PCT/US94/00093 (22) International Filing Date: 6 January 1994 (06.01.94) (30) Priority Data: 08/040,229 30 March 1993 (30.03.93) US (60) Parent Application or Grant (63) Related by Continuation US 08/040,229 (CON) Filed on 30 March 1993 (30.03.93) (71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): FOSSA, Anthony, A. [US/US]; 36 Boom Bridge Road, North Stonington, CT 06359 (US). (74) Agents: RICHARDSON, Peter, C. et al.; Pfizer Inc., Patent Dept., 235 East 42nd Street, New York, NY 10017 (US).		(81) Designated States: CA, FI, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: RADIOTELEMETRY IMPEDANCE PLETHYSMOGRAPHY DEVICE  (57) Abstract <p>A radiotelemetry device for the measurement of blood flow rates in a mammal by measuring changes in bioimpedance. The device comprises an elongated flexible catheter adapted to be inserted into a mammal's vessels, and a pair of current source electrodes and a pair of sensing electrodes disposed on the outer surface of the catheter. The pair of sensing electrodes is spaced apart along the catheter surface and disposed between the pair of current source electrodes. An implantable housing is connected to the catheter. A source of measured current is connected to the transmitting electrodes and a means for transmitting a radio signal is connected to the pair of sensing electrodes. The measured current source and the radio transmission means are contained within the housing. The device may be used advantageously in a system which comprises the above described catheter in conjunction with a receiver means for receiving the radio signal and transforming the radio signal into an electrical signal, and a signal processor means for transforming the electrical signal into a blood flow rate measurement signal.</p>		

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RADIOTELEMETRY IMPEDANCE PLETHYSMOGRAPHY DEVICE

Background of the Invention

This invention is directed to a device and system for measuring parameters
10 associated with the flow of blood in a mammal.

Prior methods of determining blood flow from body impedance changes included subjecting a body segment to a high frequency electrical current and measuring the resultant voltage variations (which directly relates to impedance variations) caused by blood flow through the body segment. The impedance method
15 of blood flow detection, often called impedance plethysmography, is based on the fact that blood has a much higher conductivity than the muscle, bone, and other tissue in the body segment. When the body segment is subjected to a high frequency electrical current, the changes in impedance are inversely proportional to the amount of blood therein.

20 For example, bioimpedance measurements are obtained by injecting a high frequency, low magnitude constant current through a segment of a patient's body by positioning a first current injecting electrode at one boundary of the body segment and a second current injecting electrode at a second boundary of the body segment. Changes in the electrical bioimpedance of the body caused by blood flow in the
25 defined body segment are detected by measuring a voltage developed across the body segment. This voltage is measured by a set of voltage sensing electrodes which are positioned on the body segment within the boundaries defined by the current injecting electrodes. Typically the electrodes are connected by wires to a standard bioimpedance measurement apparatus such as is described in U.S. Pat No. 4,450,527.

30 The electrodes may be attached directly to the skin, however it can be difficult to verify the correct and reliable connection of surface electrodes. Alternatively, (as is described in U.S. Pats. Nos. 4,852,580 and 4,836,214) the electrodes may be attached to the outside surface of an elongated, flexible catheter and connected to the bioimpedance measurement apparatus by wires that extend internally through the
35 catheter. Such catheters were designed to be inserted into the esophagus to measure blood flow through the descending thoracic aorta. These catheters obviate the problem of maintaining the proper surface electrode contact.

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In another field of art, the field of blood pressure measurement devices, catheters that contain blood pressure measuring transducers and radio transmitters have been used to transmit the blood pressure signal to a remote receiver and display device (e.g., U.S. Pat. No. 4,846,191). The advantage of this system is that it eliminates
5 the need for tethering the subject to large external power supplies. In addition, all wiring is internalized in the animal to reduce the risk of infection.

Although these various systems provide a significant advance in the field of blood flow measurement, there are still various difficulties (e.g., maintainance of surface electrode contact, required tethering of the subject to a large power supply) associated
10 with these systems. To date a flow measurement system has not been described which overcomes these problems. Accordingly, there is still a constant search in this field of art for alternative blood flow measurement systems.

Summary of the Invention

15 This invention is directed to a radiotelemetry device for the measurement of blood flow rates in a mammal by measuring changes in bioimpedance. The device comprises an elongated flexible catheter adapted to be inserted into a mammal's vessels, and a pair of current source electrodes and a pair of sensing electrodes disposed on the catheter. The pair of sensing electrodes is spaced apart along the
20 catheter and disposed between the pair of current source electrodes. An implantable housing is connected to the catheter. A source of measured current is connected to the transmitting electrodes and a means for transmitting a radio signal is connected to the pair of sensing electrodes. The measured current source and the radio transmission means are contained within the housing.

25 Another aspect of this invention is directed to a system for the measurement of blood flow rates in a mammal by measuring changes in bioimpedance. The system comprises the above described catheter in conjunction with a receiver means for receiving the radio signal and transforming the radio signal into an electrical signal, and a signal processor means for transforming the electrical signal into a blood flow rate
30 measurement signal.

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This invention provides a device capable of measuring blood flow rate (e.g., in an arterial vessel) through a relatively non-invasive procedure. It facilitates the measurement of blood flow in a conscious, free-moving animal, over a long-scale time frame, without having to perform a highly invasive procedure (e.g., thoracotomy) or have the animal tethered to a large power supply.

Other features and advantages will be apparent from the specification and claims and from the accompanying drawings which illustrate embodiments of the invention.

10

Brief Description of the Drawings

Figure 1 is a side view of an exemplary catheter of this invention.

Figure 2 is a cross-sectional view of the catheter of Figure 1 taken along line 2-2.

Figure 3 is an enlarged perspective view of the catheter depicted in Figure 1 partly broken away.

Figure 4 is an enlarged side view of the catheter illustrated in Figure 1 depicting the lengths of various catheter segments.

Figure 5 is a schematic view of the blood flow measurement system of this invention including the catheter of Figure 1 implanted in a canine artery.

20

Detailed Description of the Invention

A clearer understanding of the device may be had by reference to Figure 1. The device 3 includes a nonconductive hollow tube (catheter) 6 connected to a housing 9. Preferably the catheter 6 has sufficient rigidity that it will not kink during the introduction of the catheter 6 into the animal vessel (e.g., vein, brachial, omocervical, artery) and yet has sufficient flexibility to allow introduction into the same animal vessel (e.g., without damaging the vessel). The catheter 6 may also be contoured to reduce trauma to the vessel. The catheter 6 has a length sufficient to reach the location of the desired measurement and provide the desired bioimpedance detection. The catheter may comprise any number of biocompatible, sterilizable polymeric materials such as silicones (e.g., silastic TM silicone), polyethylenes, polyurethanes and polyvinylchlorides. The catheter 6 contains a series of spaced apart electrodes 12, 15, 18 and 21. One end 33 of the catheter 6 is preferably bullet-shaped so that catheter 6 can be easily

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inserted into a body vessel (e.g., artery, vein) and is preferably closed to prevent body fluids from entering into the hollow inner portion of the catheter 6. The flattened housing 9 contains the measured current source (e.g., a DC battery 24 and oscillator 27) and radio transmitter means 30.

5 According to Figure 2 the catheter 6 has a hollow inner cavity defined by wall 60 having an inner surface 63 and an outer surface 66. The inside diameter of the catheter 6 has a diameter sufficient so that the wires contained within (described below) are not in electrical contact. Preferably, the inside diameter of the catheter 6 is about 0.1 centimeter (cm.) to about 1 cm. The outside diameter of the catheter 6 has to be
10 compatible with the particular body vessel through which it is to be passed. Preferably the outside diameter of the catheter 6 is sufficiently small that it does not impede or alter the blood flow rate measurement (e.g., about 0.15 to about 1.25 cm.). The thickness of wall 60 should be sufficient such that, in conjunction with the particular polymeric catheter 6 material, the catheter 6 has the appropriate combination of rigidity
15 and flexibility. Catheter 6 also contains wires 69, 72, 75 and 78. These wires must not be in electrical contact. They may, for example, be separated by space or by a conventional insulating material.

Housing 9 is of a sufficient size to contain the constant current source and transmitter means and is shaped to enable the implantation in the desired animal (e.g.,
20 flattened bulb).

According to Figure 3 the catheter 6 has four electrodes 12, 15, 18, and 21 disposed on the outer surface 66 (the electrodes are in contact with the environment external to the catheter). The first electrode 12 is located proximate to the end 33 of the catheter 6. The electrode 12 is constructed from a non-corrosive, low impedance
25 conductive material so as to provide good electrical contact with the blood when the catheter 6 is inserted into the body vessel as illustrated in Figure 5. Preferably, the electrodes are titanium. The electrodes may be any form that provides the desired electrical properties, however one embodiment is a small tab (e.g., 0.1-0.5 cm²) that is imbedded in the outside surface 66 of the wall 60. Alternatively, the electrodes are
30 attached to the catheter 6 in such a manner that there is no significant disruption of the smoothness of the surface 66 of the catheter 6. Preferably, the electrodes are slightly recessed into the wall 60 and covered with a biocompatible conductive gel substance to improve the antithrombogenic (i.e. anticoagulative) qualities of the catheter. The gel

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may contain an antithrombogen (e.g., a subsystemic dose) such as is disclosed in U.S. Pat. No. 4,796,641 (e.g., heparin).

The first electrode 12 (current source electrode) is electrically connected to a first wire 100 which passes through the wall 60 (for those devices where the electrode
5 does not extend from the outside catheter surface 66 to the inside catheter surface 63) into the hollow inner portion of the catheter 6. The wire 100 is sufficiently long so that it extends from the first electrode 12 through the hollow portion of the catheter 6 to to the housing 9 where it is connected to the measured current source (e.g., DC battery 24 and oscillator 27). In an exemplary embodiment the wire 100 is an insulated, 30
10 AWG or smaller, copper wire.

A second electrode 15 is spaced apart from the first electrode 12 by a portion of the catheter 6. Typically the second electrode's composition, form, and manner of attachment to the tube 6 is the same as the first electrode 12. The second electrode 15 is utilized as a sensing electrode and thus does not carry a substantial amount of
15 current. The second electrode 15 is electrically connected to a second wire 103 which, if necessary passes through the catheter 6 wall 60 and extends through the hollow portion of the catheter 6 to the housing 9 where it is connected to the radio transmitter 30.

A third electrode 18 is spaced apart from the second electrode 15 by a portion
20 of the catheter 6. Typically the third electrode's composition, form, and manner of attachment to the tube 6 is the same as the first electrode 12. The third electrode 18 is also utilized as a sensing electrode and thus does not carry a substantial amount of current. The third electrode 18 is electrically connected to a third wire 106 which, if necessary passes through the catheter 6 wall 60 and extends through the hollow
25 portion of the catheter 6 to the housing 9 where it is also connected to the radio transmitter 30.

A fourth electrode 21 (current source electrode) is spaced apart from the third electrode 18 by a portion of the catheter 6. Typically the fourth electrode's composition, form, and manner of attachment to the catheter 6 is the same as the first electrode 12.
30 The fourth electrode 21 is electrically connected to a fourth wire 109 which, if necessary passes through the catheter 6 wall 60 and extends through the hollow portion of the catheter 6 to the housing 9 where it is also connected to the measured current source (e.g., DC battery 24 and oscillator 27).

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Figure 4 illustrates catheter 6 and the distances between the housing 9 (power supply, oscillator, radio transmitter) and respective electrodes 12,15,18 and 21. The lengths are selected to provide the desired resolution of the change in bioimpedance so that the blood flow rate can be readily determined from the radio signal. The current source electrodes 12,21 are spaced in relation to the magnitude of the current source and the size or volume of the vessel in which they are to be placed. Increased distance of these electrodes is dependent on either the increased volume of the vessel or an increased magnitude of the current used at the source. The distance L1 is typically as short as possible, preferably less than 2 cm. The lengths L2 and L4 (i.e. between the current source electrodes 12,21 and the sensing electrodes 15,18) are such that they provide adequate resolution of flow for the given vessel size. Preferably lengths L2 and L4 are about 0.1 to about 5 centimeter. The length between the sensing electrodes 15,18 (L3) is typically longer than the length between adjacent current source and sensing electrodes. Preferably the sensing electrodes 15, 18 are about 2 to about 20 centimeters apart. The length L5 from the last current source electrode 21 to the housing 9 varies according to the desired location of the flow measurement. Preferably the length of L5 is 5 to about 30 centimeters.

The foregoing dimensions of the tube 6, the electrodes and the distances between the electrodes can be readily varied in accordance with the particular application chosen (e.g., U.S. Pat. No. 4,836,214 describes appropriate measurements for placement in the aorta).

Referring now to Figure 5, the operation of the present invention for providing measurements of electrical bioimpedance will be discussed. The catheter 6 is depicted inserted into the desired vessel (e.g., a canine right common carotoid artery 201 through the aortic arch 204 and through the descending aorta 207) with the housing 9 being surgically implanted just below the skin level (the skin having been stitched over). The catheter 6 is typically inserted so that it does not touch a vessel wall along any substantial portion of the catheter 6. A measured current, preferably constant current, source of AC is provided by, for example, an appropriately sized DC battery (e.g., Rayovac® FB1225H2 lithium battery has an energy capacity of 0.8 Ampere hours at 3 Volts and is 0.62 inches square by 0.375 inches high) 24 connected to an oscillator 27 (e.g., CD4047 astable multivibrator). Preferably the frequency of the output of the current source is high enough to avoid any interference with the proper functioning of

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the electrical systems of the subject (e.g., 70 kHz). The current source contained in the housing 9 is connected to the current source electrodes 12, 21.

The current from the current source electrodes 12, 21 causes an electric field to develop between those electrodes and envelop the desired portion of the aorta 207.

- 5 The sensing electrodes 15,18 receive a voltage (the sensed signal) induced by the high frequency current flowing between the current source electrodes 12,21. This induced voltage (directly proportional to impedance; the changes in impedance are inversely proportional to the amount and velocity of blood therein) is conducted from the sensing electrodes 15,18 to the radio transmitter 30 located in the housing 9. Alternatively, an
10 amplifier and demodulator may be used to boost the sensed signal prior to being transferred to the radio transmitter.

- The radio transmitter means 30 may be any conventional radio transmitter (i.e. telemetry transmitter) that is appropriately sized (e.g., CD4047 astable multivibrator) and is capable of transmitting a signal that is a function of the sensed signal (the
15 voltage measurements). The radio transmitter 30 transforms the electrical signal into a radio signal (i.e. telemetry signal) and transmits the radio signal to a remote (i.e. external to the animal) radio receiver means RR 215. Any remote receiver capable of receiving the appropriate radio wave (e.g., Radio Shack Chronomatic model no. 12-1525) may be used. Typically an appropriate receiver would tune to the standard
20 broadcast band near 500 kilohertz. The remote receiver RR 215 transforms the radio wave to a electrical signal (e.g., digital or analog signal that is a function of the sensed signal from sensing electrodes 15,18) and conducts the electrical signal to a signal processor means SP 218 that provides a signal (that is a function of the sensed signal from sensing electrodes 15,18) to a control and display unit C+D 221.

- 25 In another embodiment a signal processor means receives the sensed signal from the sensing electrodes 15,18 or from an amplifier and provides a signal that is a function of the sensed signal (as described below) to the radio transmitter.

- The signal processor means 218 provides a measurement of blood flow rate (e.g., cardiac output) by means and calculations analogous to that described in U.S.
30 Pat. No. 4,450,527 (Sramek), the teachings of which are hereby incorporated by reference. Thus the flow rate (e.g., cardiac output) may, for example, be calculated by multiplying stroke volume times the heart beat (i.e. (liters/beat) (beats/min)). Kubicek et al., "The Minnesota Impedance Cardiography-Theory and Applications", Biochem.

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Eng. 9:410, 1974 describes an equation for the calculation of stroke volume as follows:

$$\text{Stroke volume} = (RL^2/Z_o^2)(T)(\Delta Z/\text{sec})$$

5 where R is the specific resistivity of the blood, L is the distance between the two sensing electrodes, Z_o is the base electrical impedance of the blood, T is the ventricular ejection time and $\Delta Z/\text{sec}$ is the maximum rate of impedance change with respect to time.

Alternatively, for example, a modified equation may be used as follows:

10

$$\text{Stroke volume} = (V/Z_o) (T) (\Delta Z/\text{sec})$$

where V is the physical volume of electrically participating vessel volume which approximates that of a cylinder, and the other variables are as described above. V may
15 be determined as follows:

$$V = \pi(r^2)L$$

where r is the radius of the vessel and L is the distance between the two
20 sensing electrodes. "r" may be determined by direct measurement after sacrificing the animal subsequent to taking the desired readings. Alternatively, direct measurements may be taken from a number of euthanitized animals prior to the experiment to determine a scale for future use.

In an exemplary application, the radiotelemetry device is implanted in the carotid
25 artery of a dog creating a chronic model for direct flow measurement in the descending thoracic aorta. Anesthesia and analgesia are induced in the dog and the right common carotid artery is exposed in the neck using aseptic surgical technique. The distal end of the artery is ligated and pressure is reduced with a clamp proximal to the insertion site of the catheter. A nick in the artery is made and the catheter is inserted into the
30 vessel to a predetermined distance to the descending thoracic aorta. The telemetry unit is turned on and a tracing is recorded to determine the flow at the particular site. This will aid in the final placement of the catheter. An area in the neck, preferably above scapulae, is cleared of subcutaneous fascia tissue and the telemetry unit is placed

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under the skin and sutured into position. The incision site in the neck is sutured closed and the animal is allowed to recover.

This catheter may be used for monitoring the blood flow rates of a variety of animals including mammals such as dogs, rabbits, rats and other laboratory animals
5 in addition to humans.

It should be understood that the invention is not limited to the particular embodiments shown and described herein, but that various changes and modifications may be made without departing from the spirit and scope of this novel concept as defined by the following claims.

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Claims

I claim:

- 5 1. A device for the measurement of blood flow rates in a mammal comprising:
- a. an elongated flexible catheter, said catheter adapted to be
 inserted into a mammal's vessel;
 - b. a pair of current source electrodes and a pair of sensing
10 electrodes disposed on the catheter so that they are in contact
 with the external environment;
 - c. said pair of sensing electrodes spaced apart along said
 catheter and disposed between said pair of current source
 electrodes;
 - d. an implantable housing connected to the catheter;
 - 15 e. a source of measured current connected to said current source
 electrodes, said measured current source contained within said
 housing; and
 - f. means for transmitting a radio signal connected to said pair
 of sensing electrodes, said means contained within said housing.
- 20 2. The device as recited in claim 1 wherein said current source comprises a DC
 battery connected to an oscillator.
3. The device as recited in claim 2 wherein said current source electrodes are
 positioned such that they are capable of passing a current between said current source
 electrodes through the blood.
- 25 4. The device as recited in claim 3 wherein said sensing electrodes are
 positioned such that they are capable of detecting a voltage developed across said
 sensing electrodes caused by current flowing in said blood, said voltage varying in
 accordance with changes in the electrical bioimpedance of said blood.
5. The device as recited in claim 4 wherein said electrodes are titanium.

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6. The device as recited in claim 5 wherein the catheter is formed from flexible material selected from the group consisting of silicone and polyethylene.

7. The device as recited in claim 6 wherein said sensing electrodes are about 2 to about 20 centimeters apart.

5 8. The device as recited in claim 7 wherein adjacent sensing and current source electrodes are about 0.1 to about 5 centimeters apart.

9. The device as recited in claim 8 wherein said current source electrodes are connected to said measured current source via a pair of spaced apart wires that extend internally through said catheter.

10 10. The device as recited in claim 9 wherein said sensing electrodes are connected to said signal transmission means by a pair of spaced apart wires that extend internally through said catheter.

11. A system for the measurement of blood flow rates in a mammal comprising:

- 15 a. an elongated, flexible catheter, said catheter adapted to be inserted into a mammal's vessel;
- b. a pair of current source electrodes and a pair of sensing electrodes disposed on the catheter;
- c. said pair of sensing electrodes axially spaced apart along said catheter and disposed between said pair of current source
20 electrodes;
- d. an implantable housing connected to the catheter;
- e. a source of measured current connected to said current source electrodes, said source contained within said housing;
- f. means for transmitting a radio signal connected to said pair of
25 sensing electrodes, said means contained within said housing;
- g. receiver means for receiving said radio signal and transforming said radio signal into an electrical signal; and
- h. signal processor means for transforming said electrical signal into a blood flow rate measurement signal.

30 12. The system as recited in claim 11 wherein said current source comprises a DC battery connected to an oscillator.

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13. The system as recited in claim 12 wherein said current source electrodes are positioned such that they are capable of passing a current between said current source electrodes through the blood.

14. The system as recited in claim 13 wherein said sensing electrodes are
5 positioned such that they are capable of detecting a voltage developed across said sensing electrodes caused by current flowing in said blood, said voltage varying in accordance with changes in the electrical bioimpedance of said blood.

15. The system as recited in claim 14 wherein said electrodes are titanium.

16. The system as recited in claim 15 wherein the catheter is formed from
10 flexible material selected from the group consisting of silicone and polyethylene.

17. The system as recited in claim 16 wherein said sensing electrodes are about 2 to about 20 centimeters apart.

18. The system as recited in claim 17 wherein adjacent sensing and current source electrodes are about 0.1 to about 5 centimeters apart.

15 19. The system as recited in claim 18 wherein said current source electrodes are connected to said measured current source via a pair of spaced apart wires that extend internally through said catheter.

20. The system as recited in claim 19 wherein said sensing electrodes are connected to said signal transmission means by a pair of spaced apart wires that
20 extend internally through said catheter.

21. The system as recited in claim 16 wherein said signal processor means transforms said signal from changes in electrical bioimpedance to a blood flow measurement.

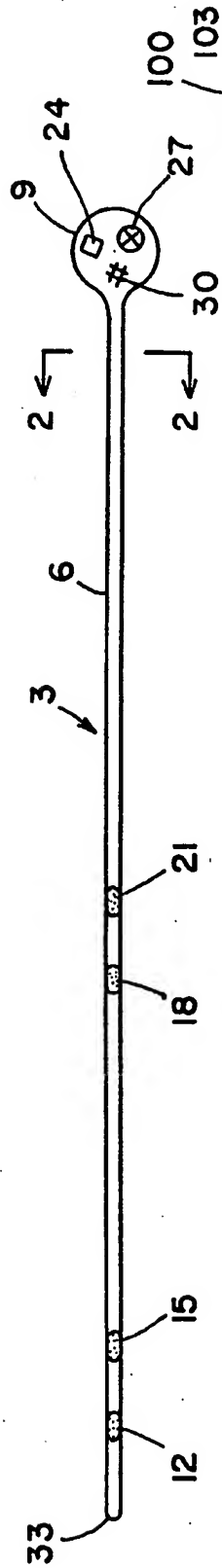


FIG. 1

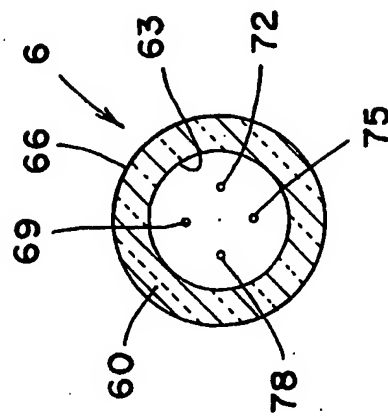


FIG. 2

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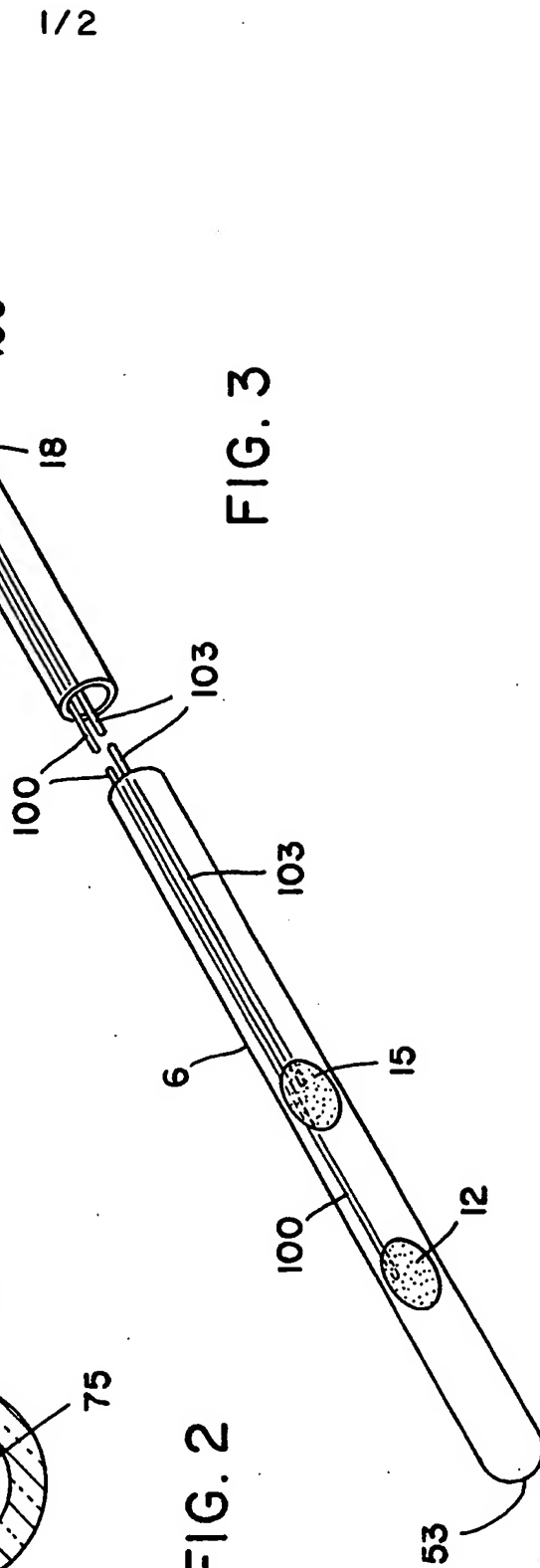


FIG. 3

2/2

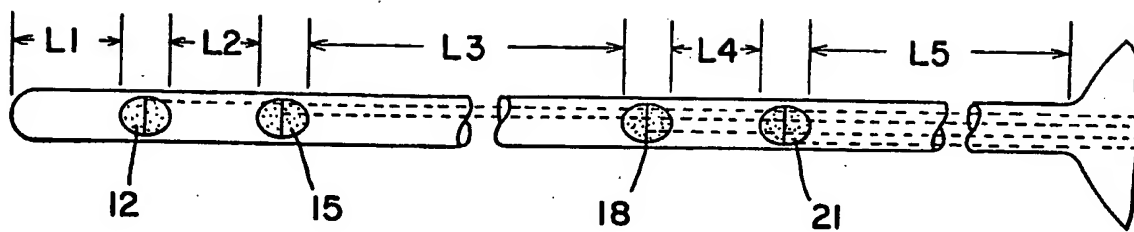


FIG. 4

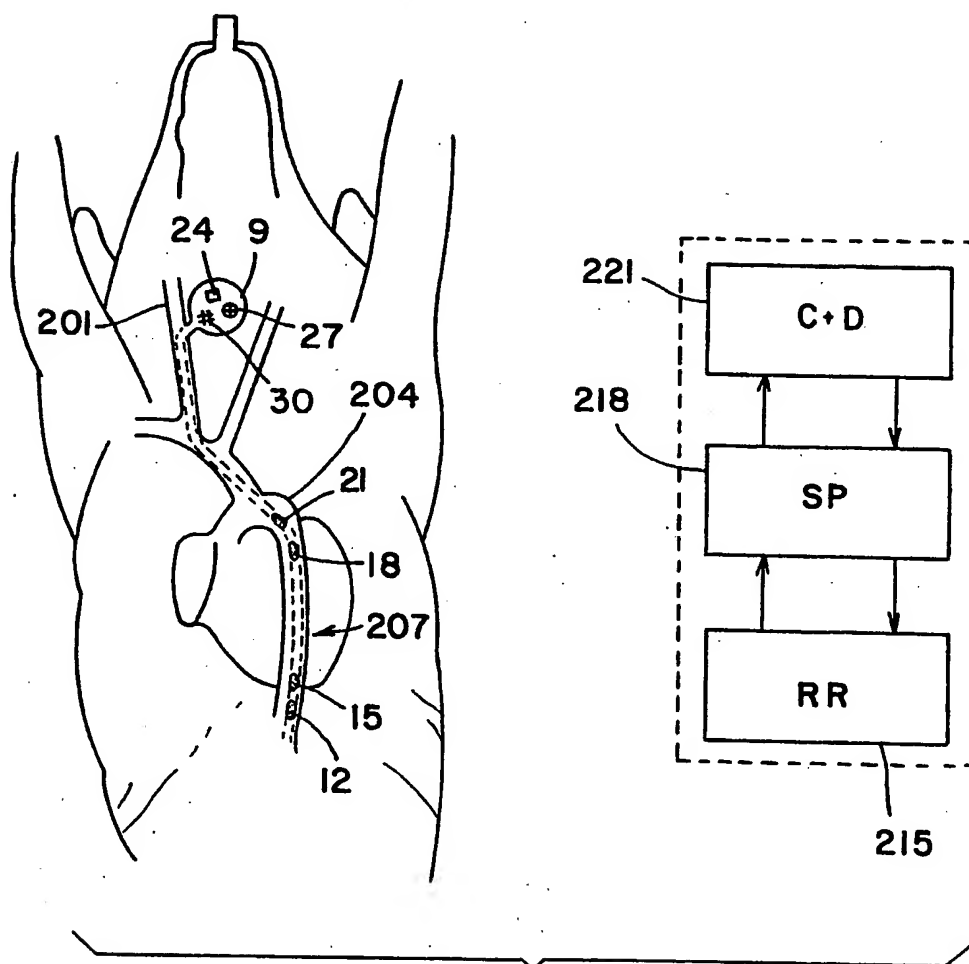


FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/00093

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 A61B5/05 A61B5/027 A61B5/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61B A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,93 02745 (MEDTRONIC INC.) 18 February 1993 see page 12, line 20 - page 13, line 3 see page 14, line 14 - page 15, line 29; figure 2 ---	1-4, 11-14
Y	EP,A,0 449 401 (CARDIAC PACEMAKERS INC.) 2 October 1991 see the whole document ---	1-4, 11-14 9,10,19, 20
A	US,A,4 543 955 (E.A.SCHROEPPEL) 1 October 1985 see the whole document ---	1,11
P,X	EP,A,0 541 338 (CARDIAC PACEMAKERS INC.) 12 May 1993 see the whole document ---	1,11
-/-		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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'&' document member of the same patent family

Date of the actual completion of the international search

3 June 1994

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 94/00093

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 310 026 (DR. E. ALT) 5 April 1989 see column 5, line 4 - column 7, line 5; figures 1,2 ---	1,11
A	US,A,4 852 580 (R.WOOD) 1 August 1989 cited in the application see the whole document ---	1,7,8, 11,17,18
A	US,A,4 796 641 (P.A.MILLS ET AL.) 10 January 1989 cited in the application see column 3, line 27 - line 59; figure 1 -----	1,6,11, 16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US 94/00093

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		AU-A- 2192492	02-03-93
		CA-A- 2089648	27-01-93
		EP-A- 0550713	14-07-93
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US-A-4543955	01-10-85	NONE	
EP-A-0541338	12-05-93	CA-A- 2082015	05-05-93
EP-A-0310026	05-04-89	DE-C- 3732640	18-05-89
		DE-A- 3881137	24-06-93
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		US-A- 4919136	24-04-90
		US-A- 5003976	02-04-91
		US-A- 4884576	05-12-89
US-A-4852580	01-08-89	NONE	
US-A-4796641	10-01-89	NONE	

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